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THE REDUCIVE AMINATION OF PHTHALALDEHYDE BY TETRACARBONYLHYDRIDOFERRATE. SYNTHESIS OF 2-ARYLISOINDOLES

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Abstract—Phthalaldehyde reacted with primary amines in the presence of tetracarbonylhydridoferrate under mild conditions to give 2-substituted isoindoles and/or isoindolines in good to excellent yields. Aliphatic amines gave selectively the isoindolines but aromatic amines had a great tendency to the isoindoles. 2-(2-Tolyl)-, 2-(4-tolyl)-, 2-(4-methoxyphenyl)-, 2-(3-chlorophenyl)-, 2-(4-chlorophenyl)- and 2-(3,4-dichlorophenyl)-isoindole were prepared by this method.

Isoindoles have been suggested to be interesting fused N-heterocycles with high reactivity, for example as conjugated dienes.[1] Although the parent isoindole has been isolated only these 6 years,[2] a variety of 2-substituted isoindoles such as 2-alkylisoindoles and 1,3- or 1,3,4,7-substituted 2-arylindoles have been prepared from isoindolines,[2-4] isoindolinones,[3] *ortho*-disubstituted benzenes,[3,5] 1,4-dicarbonyl compounds,[3,6] and unusual rearrangements of N-containing compounds.[3,7] However, only 2-phenylisoindole as simple 2-arylisoindoles has been isolated.[4b]

Described herein are the results of the reaction between phthalaldehyde and a variety of primary amines in the presence of tetracarbonylhydridoferrate as a reducing agent, affording a simple route to synthesis of 2-arylisoindoles. Aliphatic amines give selectively 2-alkylisoindolines by this procedure. The combination, glutaraldehyde-primary amine-ferrate gives a sole product, showing an excellent method for synthesis of N-alkyl- and N-aryl-substituted piperidines.[8]

The reaction between phthalaldehyde and ammonia or primary amines produces dark-colored products.[9] Major products from ammonia are isoindolinone and 3-(2-cyanophenyl)isoqunoline. Primary amines give complexed products but no isoindole derivatives. The reaction of phthalaldehyde with primary amines, however, can give 1-alkylthio-2-alkyl-substituted isoindoles when conducted in the presence of thiols.[6b]

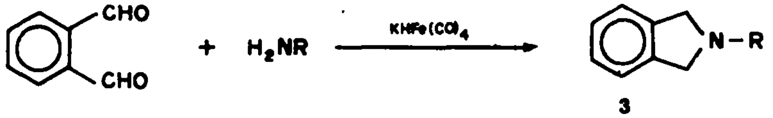
RESULTS AND DISCUSSION

The reaction of phthalaldehyde with primary amines in the presence of tetracarbonylhydridoferrate produced 2-substituted isoindoles and/or isoindolines in good to excellent yields. The results are summarized in Table 1.

The reaction proceeded under mild conditions (at room temp. under carbon monoxide) with a smooth absorption of carbon monoxide and with a rapid color change from yellowish brown to deep red. The absorption of carbon monoxide in this reaction is characteristic of the reduction by the ferrate.[10] The reducing ability of the ferrate may be equivalent with five or more hydrogens in a moist solvent with the absorption of carbon monoxide.

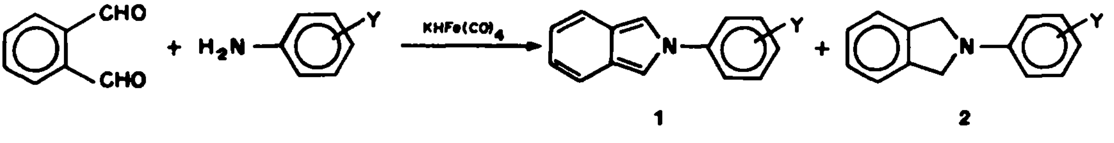
Ethylamine, benzylamine and furfuryl amine gave the corresponding 2-alkylisoindolines (3), showing that phthalaldehyde combined with aliphatic amines can be selectively derived into 3 by this method.

Aromatic amines, on the other hand, produced 2-arylisoindoles (1) and 2-arylisoindolines (2).



3

R a: CH_3CH_2
b: $PhCH_2$
c: Furfuryl



1 2

Y a: H
b: 4-CH_3
c: 3-CH_3
d: 2-CH_3
e: 4-CH_3O
f: 3-CH_3O
g: 4-Cl
h: 3-Cl
i: 2-Cl
j: 3,4-Cl_2

Table 1. The preparation of 2-substituted isoindoles and isoindolines from phthalaldehyde using tetracarbonylhydridoferrate[a]

Run	Amine	Reaction condition		Product(Yield %)		Distribution[b] %	
		Time h	CO absorbed mol/mol-ferrate			Isoindole 1	Isoindoline 2 or 3
1	Ethylamine	24	1.4	3a	30	-	100
2	Benzylamine	24	1.4	3b	65	-	100
3	Furfurylamine	24	1.3	3c	36	-	100
4	Aniline	25	1.4	1a + 2a	50	27	73
5	*p*-Toluidine	25	1.4	1b + 2b	62	56	44
5′	*p*-Toluidine	25	1.6	1b + 2b	69	95	5
6[c]	*p*-Toluidine	42	1.3	1b	73	100	-
7[d]	*p*-Toluidine	96	1.4	1b + 2b	91	65	35
8	*m*-Toluidine	45	1.9	1c + 2c	25	47	53
9	*o*-Toluidine	25	1.2	1d + 2d	31	66	34
10	*p*-Anisidine	27	1.5	1e + 2e	78	84	16
11[e]	*p*-Anisidine	26	1.6	1e	51	100	-
12	*m*-Anisidine	45	1.9	1f + 2f	63	5	95
13[e]	*m*-Anisidine	26	1.3	2f	23	-	100
14[c]	*m*-Anisidine	48	1.6	2f	69	-	100
15	*o*-Anisidine	40	1.3	Tarry material			
16	*p*-Chloroaniline	26	1.1	1g	42	100	-
17	*m*-Chloroaniline	47	1.5	1h	18	100	-
18	*o*-Chloroaniline	48	1.3	1i + 2i	20	10	90
19	3,4-Dichloroaniline	73	1.5	1j	24	100	-

a) At room temperature under carbon monoxide in moist ethanol. Molar ratio: Fe(CO)$_5$/KOH/amine/aldehyde = 1.0/3.3/1.0/1.0

b) Determined by PMR and MS.

c) Molar ratio: Fe(CO)$_5$/KOH = 1.0/3.9

d) Molar ratio: Fe(CO)$_5$/KOH = 1.0/2.7

e) Molar ratio: Fe(CO)$_5$/KOH/amije/aldehyde = 1.5/5.0/1.0/1.0

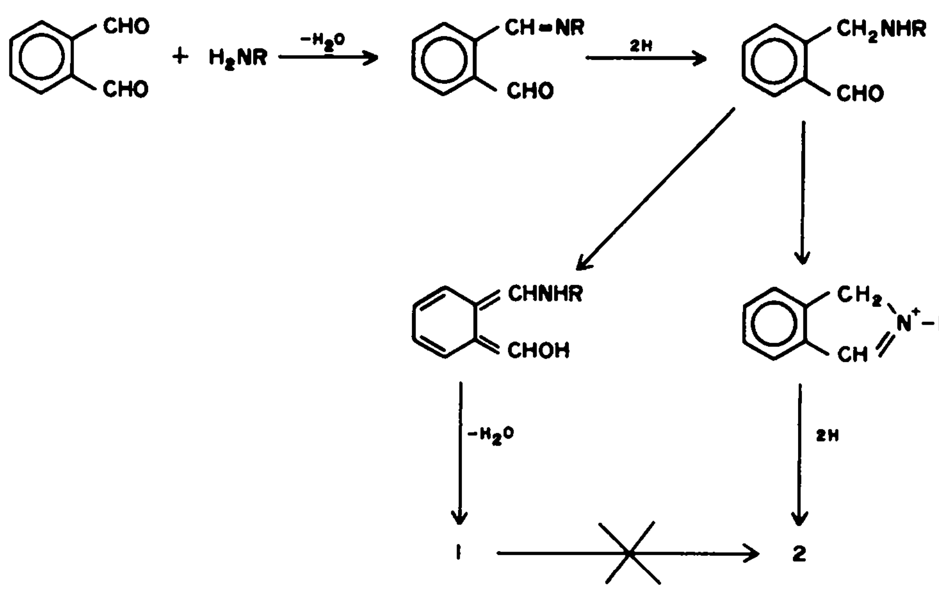
The distribution of the two products was determined by PMR and mass spectra, since the products, a mixture of **1** and **2**, were unstable for separation by tlc. The PMR study of isoindoles has shown that the methyne (C_1, C_3 and C_{4-7}) protons appear at the aromatic region.[6b] Furthermore a mass determination of isoindoles gives the only possible composition of the parent ion.[6b]

The PMR spectra of **2b** prepared from α,α′-dibromo-*o*-xylene and *p*-toluidine showed two singlets at 2.20(3H) and 4.55(4H) ppm assigned to the Me and methylene protons, respectively. The mass spectra of **2b** showed a molecular ion at 209 (rel intensity 65) and fragment ions at 208(100) and 207(8). The PMR spectra of the products from *p*-toluidine (Run 5) showed two singlets at 2.20 and 2.30 ppm assignable to the two Me groups of **2b** and **1b**, a singlet at 4.50 and a multiplet at the aromatic region. The mass spectra of the products (Run 5) showed signals at 207(100), 208(65) and 209(31). A signal with the strongest intensity at 207 appeared to be a molecular ion of **1b** and a signal at 209 was assigned to that of **2b**. On the basis of these analytical data, the distribution of the two products was calculated. The Raney Ni reduction of the products gave **2b**,[13] indicating that **1b** was reduced to **2b**.

The distribution of the products from *p*-toluidine (Runs 5–7) was highly affected by molar ratios of potassium hydroxide to iron pentacarbonyl. Higher molar ratios seemed to be favorable to the formation of **1b**, indicating that some reaction process factoring the distribution of the products has a dependency on pH. The poorly reproducible results in Run 5 and 5′ could be explained from this viewpoint that a molar ratio, KOH/Fe(CO)$_5$, was to a considerable extent higher in Run 5′ than that in Run 5.

o-Toluidine was also much favorable to the formation of **1d** but *m*-toluidine gave **2c** as the major product. In cases of anisidines and chloroanilines, the positions of substituents had great effects on the distribution of the products. The OMe group located at the *para* position has a great tendency to the corresponding isoindole (**1e**) but it has a different effect to give selectively the isoindoline (**2f**) when located at the *meta* position. *m*-Anisidine gave only **2f** even at higher molar ratio, KOH/Fe(CO)$_5$ (Run 14). From *o*-anisidine a contractable tarry material was obtained. The PMR spectra of the products from *p*-anisidine (Run 10) showed two singlets at 3.75 and 3.83 ppm assigned to the two kinds of OMe protons of **1e** and **2e**, respectively and the mass spectra showed signals at 223(100), 224(43) and 225(25). The signals at 223 and 225 appeared to be molecular ions of **1e** and **2e**, respectively. The mass spectra of the products from *m*-anisidine (Run 14) showed signals at 225(64, molecular ion of **2f**), 224(100) and 223(9).

The chloro group also has two different effects. It is



Scheme 1.

advantageous to **1** when located at the *para* and *meta* positions but to **2** at the *ortho* position. *p*-Chloro-, *m*-chloro- and 3,4-dichloroaniline gave selectively **1g**, **1h** and **1j**, respectively.

An increase in amounts of the ferrate in the reaction (Runs 10 and 11) had almost no effect on the distribution of the products. Thus, **1e** is formed as the major product even when amounts of the ferrate are enough for reduction of **1e** to **2e**. This fact suggests that **2** does not come from **1** in this reaction. Although the reaction mechanism is not clear yet, we are inclined to believe that **1** and **2** are formed from phthalaldehyde by two different routes as follows. The main reaction appears to involve the reduction of C=N bonds by the ferrate.

The results obtained here indicate that simple 2-arylisoinoles can be readily prepared from phthalaldehyde by this procedure.

EXPERIMENTAL

All ^{1}H NMR chemical shifted are given in parts per million from added Me_4Si in $CDCl_3$ and were recorded on a JEOL JNM-PM-60 spectrometer. Mass spectra were taken on a JEOL 01SG mass spectrometer. IR spectra were measured with a 215 Hitachi spectrometer. All m.ps were taken on a Yanagimoto apparatus and are uncorrected.

Materials. Phthalaldehyde, primary amines, iron pentacarbonyl and solvents were all commercial products and were used without further purification. Potassium tetracarbonylhydridoferrate was prepared accordingly to the method described in a previous paper.[11] 2-(*p*-Tolyl)-isoindoline was prepared from *α,α'*-dibromo-*o*-xylene and *p*-toluidine.[12]

General reaction procedure. To a mixture of iron pentacarbonyl (11 mmmol), ethanolic 1 M-KOH (33 mmmol) and a primary amine (11 mmol) was added phthalaldehyde (11 mmol) and the mixture was stirred at room temp. under CO for 24–96 hr. Crystalline compounds gradually separated. The crystals were collected by filtration and purified by recrystallization from hot EtOH. In cases of ethylamine, benzylamine, furfurylamine, *o*-toluidine and *o*-chloroaniline, the filtered mixture was exposed to air for 2 or 3 days and concentrated to about 5 ml at 40°/30 Torr and then products were separated by vacuum distillation.

The products were analyzed by means of IR, PMR and MS spectra and elemental analyses. All the 2-substituted isoindolines are known compounds and were identified by PMR spectra. All the 2-arylisoindoles except **1a** are unknown compounds. Although the reaction products, a mixture of **1** and **2** were unstable for separation by tlc, the distribution of the products can be determined by comparing the chemical shifts of the methylene (C_1 and C_3) protons of **2** (δ 3.8–4.8 ppm, s) and the methyne (C_1, C_3 and C_{4-7}) protons of **1** (at the aromatic region).[6b]

2-*Aryl-isoindoles* (**1**) *and/or -isoindolines* (**2**). Aromatic amines gave **1** and/or **2** as colorless crystals or liquids.

2-(p-*Tolyl*)*isoindoline* (**2b**) was prepared from *α,α'*-dibromo-*o*-xylene.[12] PMR($CDCl_3$): δ (ppm) 2.20 (s, 3H, CH_3), 4.55 (s, 4H, CH_2–N), 6.5–7.5 (m, 8H). MS *m/e*: 209 (rel intensity 65, M^+), 208(100), 207(8).

2-(p-*Tolyl*)*isoindole* (**1b**) *and* **2b** (Run 5). M.p. 184–186°, yield 62%. PMR($CDCl_3$): δ 2.20 (s, CH_3 of **2b**), 2.30 (s, CH_3 of **1b**), 4.50 (s, CH_2–N of **2b**), 6.3–7.7 (m). MS *m/e*: 207(100, M^+ of **1b**), 208(65), 209(31, M^+ of **2b**). Found: C, 85.89; H, 6.95; N, 6.67. Calc. for $C_{15}H_{13}N$ (as **1b**): C, 86.88; H, 6.32; N, 6.75%. By comparing the PMR and mass spectra, the distribution of **1b** and **2b** was determined to be 56 and 44%, respectively.

Compounds **1b** *and* **2b** (Run 5'). M.p. 177–181°, yield 69%, **1b**:**2b** = 95%:5%. MS *m/e*: 207(100, M^+ of **1b**), 208(21), 209(5). Found: C, 86.73; H, 6.44; N, 6.71%.

2-*Phenylisoindole* (**1a**) *and -isoindoline* (**2a**) (Run 4). M.p. 169–171°, yield 50%. PMR($CDCl_3$): δ 4.55 (s, CH_2–N of **2a**), 6.5–7.5 (m).

2-(m-*Tolyl*)-*isoindoles* (**1c**) *and -isoindoline* (**2c**) (Run 8). M.p. 84–85° (dec), yield 25%. PMR($CDCl_3$): δ 2.25 (s, CH_3 of **2c**), 2.35 (s, CH_3 of **1c**), 4.55 (s, CH_2–N of **2c**), 6.5–7.5 (m).

2-(o-*Tolyl*)-*isoindole* (**1d**) *and -isoindoline* (**2d**) (Run 9). B.p. 94°/0.3 Torr. PMR($CDCl_3$): δ 2.15 (s, CH_3 of **2d**), 2.45 (s, CH_3 of **1d**), 4.55 (s, CH_2–N of **2d**), 6.8–7.8 (m).

2-(4-*Methoxyphenyl*)-*isoindole* (**1e**) *and -isoindoline* (**2e**) (Run 10). M.p. 194–197°. PMR($CDCl_3$): δ 3.75 (s, CH_3O of **1e**), 3.85 (s, CH_3O of **2e**), 4.55 (s, CH_2–N of **2e**), 6.5–7.5 (m). MS *m/e*: 223(100, M^+ of **1e**), 224(43), 225(25, M^+ of **2e**), 208(68). Found: C, 80.51; H, 5.91; N, 6.23. Calc. for $C_{15}H_{13}NO$ (as **1e**): C, 80.69; H, 5.87; N, 6.27%.

2-(3-*Methoxyphenyl*)*isoindoline* (**2f**) (Run 14). M.p. 115–117°. PMR($CDCl_3$): δ 3.75 (s, 3H), 4.55 (s, 4H), 6.2–7.5 (m, 8H). MS *m/e*: 225(64, M^+ of **2f**), 224(100), 223(9).

2-(4-*Chlorophenyl*)*isoindole* (**1g**) (Run 16). M.p. 194–197°. PMR($CDCl_3$): δ 6.1–7.6 (m). MS *m/e*: 227(100, M^+ of **1g**), 229(33). Found: C, 73.81; H, 4.55; N, 6.20. Calc. for $C_{14}H_{10}ClN$ (as **1g**): C, 73.85; H, 4.43; N, 6.15%.

2-(3-*Chlorophenyl*)*isoindole* (**1h**) (Run 17). M.p. 119–120° (dec). PMR($CDCl_3$): δ 6.1–7.5 (m). Found: C, 73.74; H, 4.83; N, 6.10%.

2-(2-*Chlorophenyl*)-*isoindole* (**1i**) *and -isoindoline* (**2i**) (Run 18).

B.p. 117°/0.2 Torr. PMR($CDCl_3$): δ 4.80 (s, CH_2–N of **2i**), 6.5–7.6 (m).

2-(3,4-*Dichlorophenyl*)*isoindole* (**1j**) (Run 19). M.p. 132–133.5°. PMR($CDCl_3$): δ 6.7–8.1 (m). MS *m/e*: 261(100, M^+ of **1j**), 263(63), 265(13). Found: C, 64.43; H, 3.62; N, 5.14. Calc. for $C_{14}H_9Cl_2N$ (as **1j**): C, 64.15; H, 3.46; N, 5.34%.

2-*Alkylisoindolines* (**3**). The filtered and concentrated mixture gave 3 by vacuum distillation. **3a**, b.p. 56°/1 Torr. PMR($CDCl_3$): δ 1.20 (t, 3H), 2.74 (q, 2H), 3.88 (s, 4H), 7.10 (s, 4H). **3b**, b.p. 110°/0.1 Torr. PMR($CDCl_3$): δ 3.9 (s), 3.85 (s), 7.05–7.5 (m). **3c**, b.p. 86°/0.2 Torr. PMR($CDCl_3$): δ 3.95 (s, 4H), 3.85 (s, 2H), 6.1–6.3 (m, 2H), 7.05–7.5 (m, 5H).

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[13] The products (0.5 g, **1b** and **2b**) from *p*-toluidine in Run 5 were stirred at 60° under pressures of hydrogen (5 atm) for 6 hr in EtOH (20 ml) in the presence of the Raney Ni (W-2, 0.3 g). The filtered mixture gave colorless crystals (0.45 g, **2b**), which were recrystallized from EtOH and identified by means of IR and PMR spectra.